
REGIONAL CEREBRAL BLOOD FLOW IN PATIENTS WITH ALCOHOL-RELATED DEMENTIA: A SPECT STUDY

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The purpose of this study was to investigate regional cerebral blood flow (rCBF) changes using 1110 MBq of Tc-99m ECD SPECT in alcohol-related dementia (ARD) patients. Twenty-five patients with ARD and 22 healthy control subjects were included in the study. Mini-Mental Status Examination was applied to the patients and controls. The ARD patients showed drastically reduced rCBF in the frontal cortices, basal ganglia, and thalami. The results indicate that ARD is associated with hypoperfusion in both cortical and subcortical regions. These findings support previous studies suggesting the association with both cortical and subcortical neuropathology in ARD patients.

Keywords alcohol dependence, alcohol-related dementia, cerebral blood flow, cortical and subcortical regions, hypoperfusion, SPECT

INTRODUCTION

Alcohol consumption is prevalent worldwide and can result in major health issues causing innumerable social and economic problems. In particular, long-term chronic alcohol consumption is associated with damage in corresponding neural substrates and cognitive deficits including memory impairment, and with excessive alcohol consumption an increased risk of dementia (Reed et al., 2003; Shear, Jernigan, & Butters, 1994). The major psychiatric features of alcoholic dementia are global, persisting and disabling cognitive impairment, which

persist during abstinence. Many studies have shown that alcoholic dementia ensues from the neurotoxic effect of alcohol (Harper & Matsumoto, 2005; Nicolas et al., 1993). There have been neuroimaging studies that focused on regional cerebral blood flow (rCBF) changes in chronic alcoholic patients, and their main common findings were frontal hypoperfusion (Dao-Castellana et al., 1998; Erbas et al., 1992; Kuruoglu et al., 1996; Melgaard et al., 1990; Moselhy, Georgiou, & Kahn, 2001). Furthermore, abnormal rCBF changes (e.g., decrease) in frontal regions of the brain were seen using positron emission tomography (PET) (Gilman et al., 1990). Studies have shown that the long-term use of alcohol decreases the metabolic rates and rCBF changes but no study has directly focused on the dementia resulting from alcohol consumption. The purpose of this study was to investigate rCBF changes using 1110 MBq of Tc-99m ECD single photon emission computed tomography (SPECT) in alcohol related dementia (ARD) patients who were diagnosed by the criteria presented by Oslin et al. (Oslin, Atkinson, Smith, & Hendrie, 1998; Oslin & Cary, 2003).

METHODS

Subjects

Twenty-five male patients were enrolled in the study (see Table 1) with probable ARD according to criteria presented by Oslin et al. (1998). We included only men to rule out the differences between sexes. The average period between the last drink and the start of treatment was 78.9 days (range 62–98 days). All patients were selected based on the following inclusion and exclusion criteria. *Inclusion criteria:* (1) cognitive dysfunction with a mini mental state examination (MMSE) score \leq 23 (Folstein, Folstein, & McHugh, 1975; Kwon & Park, 1989), (2) past history of significant alcohol use as defined as a minimum average of 35 standard drinks per week for men for a period of more than 5 years, (3) significant alcohol use within 3 years of initial onset of dementia, and (4) at least a 60-day abstinence period before clinical diagnosis. *Exclusion criteria:* (1) any DSM-IV Axis I disorder not defined in the inclusion criteria except alcohol-related disorders, (2) one or more episode of seizure without a clear and resolved etiology, (3) language impairment, especially dysnomia or anomia, (4) focal neurological signs or symptoms (except ataxia, or peripheral sensory polyneuropathy), (5) greater than 4 on the modified Hachinski Ischemia scale score, (6) pregnant or lactating, and (7) judged clinically to be at serious suicidal risk.

Table 1. Demographic and clinical characteristics of the study population

Variables	Patients (<i>N</i> = 25)	Control (<i>N</i> = 22)	<i>p</i>
Age (years)	60.44 ± 7.43	56.1 ± 8.7	.304
Gender (male/female)	25/0	22/0	
Education (years)	7.85 ± 3.73	10.0 ± 5.1	.070
1st onset of drinking (years)	18.65 ± 3.15	19.9 ± 2.8	.840
Onset of problematic drinking (years)	47.48 ± 9.21		
1st age of admission in psychiatric hospital (years)	55.19		
Number of admissions in psychiatric hospital	2.77 ± 1.63		
Frequency of drinking (per week)	5.38 ± 1.27	1.1 ± 0.4	>.000
Number of drinks per occasion (SD)	14.81 ± 5.74	2.02 ± 0.5	>.000
MMSE	20.28 ± 0.54	28.7 ± 1.2	>.000
CDR	1.71 ± 0.59	1.0 ± 0	>.000
GDS	4.89 ± 0.81	1.0 ± 0	>.000

Values are given as mean ± standard deviation. *p*: statistical differences on a significant level, using independent *t*-test; SD: standard drink; MMSE: mini mental state examination; CDR: clinical dementia rating scale; GDS: global deterioration scale.

Most patients had one or more medical diseases such as alcohol-related hepatic diseases (42%) confirmed by use of abdominal ultrasonography, diabetes mellitus (26%), hypertension (21%), respiratory diseases (15%), and other disease (13%). All patients were free from pathologic brain lesions including evidence of previous stroke, brain atrophy, or space-occupying mass on brain MRI at admission.

As a comparison group, 22 male nonalcoholic control subjects were included in this study (mean age: 56.1 ± 8.7 years, age range: 41–67 years).

Procedures

The general cognitive state was determined by a Korean version of the MMSE) and the clinical dementia rating scale (CDR) (Hughes, Berg, Danziger, Coben, & Martin, 1982), along with the global deterioration scale (GDS) in order to evaluate the severity of dementia. The sample consisted of inpatients of Holy Family Hospital, College of Medicine, the Catholic University of Korea, and

admitted for detoxification, evaluation, and treatment of alcohol dependence. All subjects who participated in this study provided written informed consent, and this study was approved by the IRB of the Catholic University of Korea.

SPECT Image Acquisition and Analysis

SPECT images were obtained 40 min after intravenous injection of 1110 MBq of Tc-99m ECD using a dual-head gamma camera (ECAM plus; Siemens, Erlangen, Germany) equipped with a low-energy, fan-beam collimator. Subjects were supine with eyes open during the scan. The room was dimly lit and noise was kept to a minimum. Data were reconstructed in a 128×128 matrix with a pixel size of $3.9 \times 3.9 \times 3.9$ mm (FOV = 240 mm, slices thickness = 7 mm), and a 20% symmetric window at 140 keV. Continuous transaxial tomograms of the brain were reconstructed after back projection with a Butterworth filter (cutoff frequency 0.4 cycles/pixel, order 5) to reduce statistical noise. Tc-99m ECD images were corrected for tissue attenuation using a standard commercial correction routine (Siemens, Erlangen, Germany).

Image manipulation and data analyses were performed on an IBM personal computer running Windows XP operating system. SPM2 software based on MatLab version 6.0 was used for image analyses. The SPECT data with attenuation and scatter correction were converted into an analyzable format. The mean pixel intensity across all slices of the imaging volume was calculated. Each voxel was fixed at 80% threshold of the value to eliminate background noise and partial volume effects at the edge of the brain. Each SPECT scan was then spatially normalized using a 12-parameter affine warping and sinc-linear interpolation to the SPECT template brain from the Montreal Neurological Institute, reformatted to a 16-bit image of $79 \times 95 \times 68$ voxels, each $2 \times 2 \times 2$ mm in size. These images were spatially smoothed with a Gaussian filter of 16 mm full-width at half maximum (FWHM). Normalized rCBF values were calculated by dividing cerebral blood flow (CBF) at each voxel by global CBF in each individual. The t -statistic image was threshold at $t = 3.96$, corresponding to a corrected p -value $< .05$, in conjunction with a cluster filter of 100 voxels. This combined application of statistical threshold and cluster filter has been shown previously to substantially reduce the false positive identification of activated pixels at any given threshold. The t -score clusters were projected onto the standard high-resolution T1-weighted MRI for anatomic localization and visualization.

Statistical Analyses

All analyses for demographic variables were performed using SPSS version 12.0 for windows. The significance level was set at $p < .05$ with familywise error (FEW) correction.

RESULTS

All subjects showed diffusely decreased patterns of rCBF compared with the controls. rCBF in all subjects was drastically reduced over the frontal cortices, basal ganglia, and thalami. Also, diminished rCBF was noted in some parietal and temporal cortices. When the ARD group was compared with the control group through statistical parametric mapping (SPM) without global normalization, overall diffuse decrement in CBF was demonstrated in the ARD group. Using global normalization in SPM, massive reductions in rCBF were detected in ARD in both corpus callosum, pulvinar of right thalamus, cingulate gyri of both limbic lobe (BA 23, BA 24, BA 32), both caudates, left insula (BA 13), right cerebellum, left middle frontal gyrus (Frontal Gyrus, BA 8), both inferior parietal lobules (BA 40), postcentral gyrus of left parietal lobe, right inferior frontal gyrus (BA 47), and right superior temporal gyrus (see Table 2, Figure 1). In addition, the mean global count of the ARD group was computed as 83.47 ± 7.56 , and as 120.40 ± 11.12 in the control group. The rCBF difference of two groups was statistically significant. ($p < .0001$)

DISCUSSION

Many previous studies (Dao-Castellana et al., 1998; Erbas et al., 1992; Melgaard et al., 1990) have shown that alcoholism is associated with hypoperfusion in the frontal region, and other findings (Bowden, 1990) emphasized the importance of medial frontal and cingulate cortices in understanding the neurobiology of alcoholism. Additionally, alcoholics in the previous studies (Demir, Ulug, Lay Ergun, & Erbas, 2002; Moselhy et al., 2001) exhibited almost identical patterns of neuropsychological abnormalities that were mainly related to frontal lobe functions. Neuropathological studies have identified alcohol-related neuronal loss in superior frontal association cortex, hypothalamus, and cerebellum (Harper, 2009; Harper & Kril, 1990), although other studies reported a relationship between maximum daily alcohol consumption and the amount of white matter volume loss (Kril, Halliday, Svoboda, & Cartwright, 1997).

Table 2. Location of disproportionately decreased rCBF in ARD compared with normal control

Cluster k_E	Voxel					Brain area
	<i>t</i> -value	<i>z</i> -value	<i>x</i>	<i>y</i>	<i>z</i>	
17832	7.96	6.32	4	-32	12	Right corpus callosum
17832	7.36	5.99	14	-24	16	Right thalamus, pulvinar
17832	6.67	5.58	-12	-40	20	Left corpus callosum
17832	6.35	5.39	-2	20	32	Left limbic lobe, cingulate gyrus, BA 32
17832	6.34	5.38	4	-34	26	Right limbic lobe, cingulate gyrus, BA 23
17832	6.11	5.23	-14	12	12	Left caudate body
17832	6.05	5.19	-2	10	32	Left limbic lobe cingulate gyrus, BA 24
17832	5.99	5.15	-28	-28	20	Left insula, BA 13
17832	5.46	4.79	12	2	16	Right caudate body
17832	5.22	4.62	6	12	4	Right caudate head
403	5.02	4.48	10	-66	-38	Right cerebellum, posterior lobe
309	4.76	4.28	-50	20	38	Left middle frontal gyrus, BA 8
1308	4.71	4.25	-56	-36	40	Left inferior parietal lobule, BA 40
1308	4.70	4.24	-56	-34	48	Left parietal lobe, postcentral gyrus
342	4.47	4.06	48	-38	54	Right inferior parietal lobule, BA 40
290	4.16	3.83	42	16	-8	Right inferior frontal gyrus, BA 47
290	4.16	3.82	24	14	-26	Right superior temporal gyrus

t = 3.96; corrected *p* < .05; voxel size: 100.

However, previous studies have focused on the alcohol-dependent patients or chronic alcohol-dependent patients, and there have been few studies that focused on alcoholic dementia patients who were diagnosed by objective diagnostic criteria. Additionally, there have been very few imaging studies using SPECT for these patients. Although there has been evidence that alcohol use may have direct neurotoxic effects leading to the characteristic dementia syndrome of ARD, this is not a universally accepted concept. The lack of consistent neuropathological findings associated with alcohol use has led some authors to cast doubt on the clinical relevance of any direct neurotoxic effects

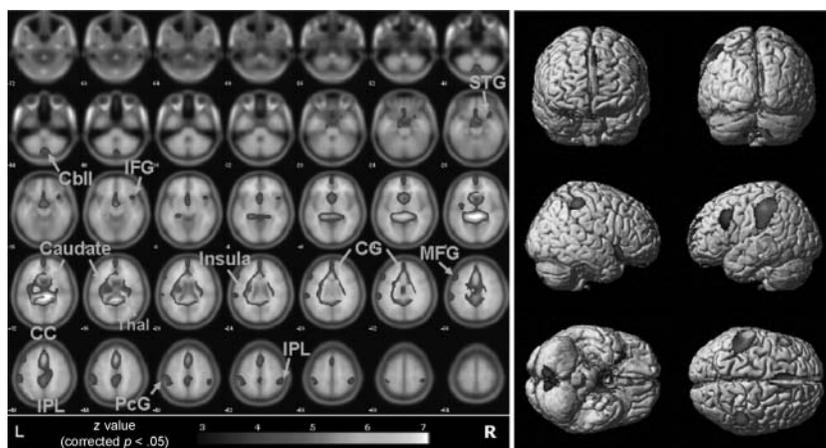


Figure 1. Group differences in ARD comparing with normal control. The brain regions are shown where normalized rCBF values are disproportionately reduced in the alcohol-related dementia patients compared with the healthy control subjects. The numbers on the left-most margin of each row are locations of the axial slices (z -levels) in the Talairach atlas. t -values are color-coded according to the color bar in the lower corner of the figure. Magnitude threshold $t = 3.96$, $p < .05$, and cluster filter = 100 voxels, each $2 \times 2 \times 2$ mm in size after spatial normalization. MFG: middle frontal gyrus, SFG: superior frontal gyrus, CG: cingulate gyrus, STG: superior temporal gyrus, Cbll: cerebellum, IFG: inferior frontal gyrus, CC: corpus callosum, Thal: thalamus, IPL: inferior parietal lobule, PcG: parietal lobe, postcentral gyrus.

of alcohol use. Authors, such as Victor, have cast doubt on the existence of primary alcoholic dementia, suggesting that dementia in alcoholics is secondary to Wernicke-Korsakoff syndrome, malnutrition, vascular dementia, hepatic disease, or coincident Alzheimer's dementia (Victor, 1993).

In addition, the current vague criteria including DSM-IV limit the ability to collect cases reliably and compare studies. Moreover, many of the studies relating alcohol use to cognitive or neuropathological changes present limited clinical correction and often do not specifically include patients with dementia. Although the diagnosis of ARD is somewhat controversial as mentioned above (Victor, 1993), Oslin et al. (1998) proposed a diagnostic scheme and criteria for ARD. Oslin's criteria were proposed for the purposes of improving the validity and reliability of the diagnosis of ARD in order to reduce subjective interpretation and standardize alcohol consumption criteria (Oslin & Cary, 2003). Schmidt et al. (2005) reported that the neuropsychological profile of ARD suggested cortical and subcortical pathology using the criteria presented by Oslin et al. (1998). In addition, Moriyama mentioned that the criteria by Oslin

et al. represented a purer form of alcoholic dementia and were useful for the scientific discussion of this condition (Moriyama, Mimura, Kato, & Kashima, 2006). We agreed with this concept and adopted the diagnostic criteria for ARD outlined by Oslin et al. (1998) in the present study. Therefore, in this study we could examine the rCBF abnormalities in relatively homogeneous ARD patients who could be distinguished from the patients in the previous studies.

Not surprisingly, all subjects showed diffusely decreased patterns of rCBF compared with controls. rCBF in all subjects was drastically reduced over the frontal cortices, basal ganglia, and thalami. The global normalization using SPM was performed because the baseline changes in rCBFs in the patient group and the control group were significantly different. In other words, before global normalization, we showed that there was a significant difference in the rCBF between the two groups. However, using global normalization we could specify the regions with rCBF changes in the two groups. Previous neuroimaging studies have related chronic alcohol abuse with generalized volume reductions in cortical and subcortical gray and white matter, though regional specificity of the brain varies across studies (Harper, 1998; Reed et al., 2003; Shear et al., 1994). ARD might be associated with both cortical and subcortical neuropathology based on the neuropsychological tests (executive function and memory) that focused on ARD patients (Nicolas et al., 1993; Schmidt et al., 2005). These findings may be somewhat different from the results of previous studies mainly related to frontal lobe pathology in alcoholism patients.

Although there is a consensus concerning the deleterious effects of chronic alcohol consumption on cognition, the question remains as to the exact pathophysiology or mechanism of alcoholic dementia. Chronic exposure to ethanol causes adaptive upregulation in sensitivity of *N*-methyl *D*-aspartate (NMDA) receptors, which can result in an increased vulnerability for glutamate-induced excitotoxicity. This excitotoxic insult is one of the most important factors in the mechanism underlying ethanol-induced brain damage (Harper & Matsumoto, 2005).

This study has some limitations. First, the sample size was small and did not allow the identification of more specific significant differences between ARD and normal controls. Secondly, the utilization of the criteria presented by Oslin et al. (1998) does not rule out the presence of Wernicke-Korsakoff syndrome and Alzheimer's disease in ARD patients. However, the inclusion criteria in our study had no history of an acute onset of symptoms linked with Wernicke's encephalopathy. In addition, the current follow-up information on the ARD patients suggests that clinical findings and neurocognitive symptoms may at

least remain stable in the ARD patients following abstinence from alcohol. This is not likely in other types of dementia, such as Alzheimer's disease. Third, we did not have the SPECT results of subjects with alcohol dependence without neurocognitive impairment and other serious physical complications in the study, so in future we will need additional research to describe the effect of alcohol in subjects with alcohol dependence without dementia. Fourth, the findings of brain perfusion SPECT generally reflect the rCBF of gray matter in the brain. Therefore, it is difficult to find brain atrophy in the periventricular region by SPECT imaging. According to Nicolas's previous study on chronic alcoholism using SPECT, both atrophic alcoholics and non-atrophic alcoholics showed significant hypoperfusion of the frontal lobes (Nicolas et al., 1993). However, we wanted to minimize the possibility that the results in our study were a reflection of atrophy and to find purer form of ARD patients. For this reason, we excluded all patients who had pathological brain lesions (including the evidence of previous stroke) and severe brain atrophy on brain MRI at admission and matched age–sex of the ARD patients with that of control subjects.

In conclusion, our results suggest that ARD may be associated with both cortical and subcortical neuropathology based on neuroimaging findings using SPECT. Currently, many dementia neuroimaging studies are under progress and demonstrate different results among Alzheimer's disease, subcortical vascular dementia, and mild cognitive impairment patients. Our study contributes to the neuroimaging literature of dementia patients in that it can be considered as a possible option regarding dementia from the use of the alcohol. Further work using both neuropsychological and neuroimaging methods are recommended in large samples of ARD patients for the replication of our findings.

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